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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/550,608 | 12/14/2006 | Antonio Martinez Martinez | ABG 3008 | 1313 |

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| EXAMINER | |
|---|---|
| LEE, JAE W | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1656 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 02/28/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mail@krameramado.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/550,608 | MARTINEZ ET AL. | |
| | Examiner | Art Unit | |
| | JAE W. LEE | 1656 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *15 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,4,6-12 and 30-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-12 and 30-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 September 2005 and 07 January 2010* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/15/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Application status*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/15/2010 has been entered.

In response to the previous Office action, a Final rejection (mailed on 04/15/2010), Applicants filed a response received on 07/15/2010. Claims 1, 4, 6-12 and 30-38 are at issue and present for examination.

Applicants' arguments filed on 07/15/2010, have been fully considered, and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

### *Information Disclosure Statement*

The information disclosure statement filed on 07/15/2010 is acknowledged. The reference cited therein has been considered.

***Claim Rejections - 35 U.S.C. § 112***

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The previous rejection of Claims 30-38 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn because Applicants' argument has been found persuasive.

***Claim Rejections - 35 U.S.C. § 103***

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of Claims 1, 4 and 6-12 under 35 U.S.C. 103(a) as being unpatentable over Cappellan et al. (Frequent Activating Mutations of FGFR3 in Human B adder and Cervix Carcinomas, Nature Genetics, Vol. 23, September 1999, see IDS) in view of KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007) and an evidentiary reference of Sturla et al. (FGFR3IIIS: a novel soluble FGFR3 spliced variant that modulates growth is frequently expressed in tumour cells, British Journal of

Cancer (2003) 89, pages 1276 – 1284, published online on 09/30/2003) is withdrawn in favor of a new rejection as shown below.

Claims 1, 4, 6-12 and 30-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Monia et al. (US Patent Application No. 09/953,047 filed on 09/10/2001) in view of Cappellan et al. (Frequent Activating Mutations of FGFR3 in Human B adder and Cervix Carcinomas, Nature Genetics, Vol. 23, September 1999, see IDS), KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007) and an evidentiary reference of Sturla et al. (FGFR3IIIS: a novel soluble FGFR3 spliced variant that modulates growth is frequently expressed in tumour cells, British Journal of Cancer (2003) 89, pages 1276 – 1284, published online on 09/30/2003).

Claims 1, 4, 6-12 and 30-38 are drawn to an *in vitro* method [i] to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or [ii] to assess the stage or severity of bladder TCC in an individual, that comprises: a) the detection and/or quantification of the FGFR3 protein in a sample of an individual, wherein the sample is a bladder tissue or urine, and b) the comparison of the amount of FGFR3 protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3-protein relative to normal reference values are indicative of bladder TCC, and normal reference values in samples are from subjects without bladder transitional cell carcinoma.

It is noted by the Examiner that the specification does not define the term "FGFR3", and therefore, it has been interpreted according to Applicants' remarks as

encompassing "the normal forms of the FGFR3 protein, FGFR3IIIc and FGFR3IIIb" (see Applicant's remarks filed on 01/07/2010, page 12, lines 15-17).

Monia et al. teach a method of detecting or quantifying the FGFR3 protein in a sample via Western blot analysis using appropriate primary and secondary antibodies against FGFR3 protein (see Example 16 on page 86 of the specification). Monia et al. further teach that:

"[p]rotein levels of fibroblast growth factor receptor 3 can be quantitated in a variety of ways well known in the art, such as immunoprecipitation, Western blot analysis (immunoblotting), ELISA or fluorescence-activated cell sorting (FACS). Antibodies directed to fibroblast growth factor receptor 3 can be identified and obtained from a variety of sources, such as the MSRS catalog of antibodies (Aerie Corporation, Birmingham, MI), or can be prepared via conventional antibody generation methods." Monia et al. further teach that "[m]ethods for preparation of polyclonal antisera are taught in, for example, Ausubel, F.M. et al., Current Protocols in Molecular Biology, Volume 2, pp. 11.12.1-11.12.9, John Wiley & Sons, Inc., 1997", while "[p]reparation of monoclonal antibodies is taught in, for example, Ausubel, F.M. et al., Current Protocols in Molecular Biology, Volume 2, pp. 11.4.1-11.11.5, John Wiley & Sons, Inc., 1997" (see 2nd paragraph on page 77 of the specification).

Monia et al. teach the use of antisense oligonucleotides to decrease or inhibit the expression of FGFR3 protein because "FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype" (see lines 31-34 on page 1 of the specification).

Monia et al. do not teach bladder TCC.

Cappellan et al. teach that:

[t]he expression of a constitutively activated FGFR3 in a large proportion of two common epithelial cancers is the first evidence of an oncogenic role for FGFR3 in carcinomas. FGFR3 currently appears to be the most frequently mutated oncogene in bladder cancer: it is mutated in more than 30% of cases. FGFR3 seems to mediate

opposite signals, acting as a negative regulator of growth in bone and as an oncogene in several tumour types (see page 19, center column, 2nd paragraph).

Cappellan et al. further teach that they "assessed transcript levels of the two FGFR3 variants, FGFR3b and FGFR3c, [which are identical to what Applicants refer to as FGFR3IIIb and GFGR3IIIc, respectively] by semi-quantitative RT-PCR in 76 primary bladder carcinomas, 6 normal urothelia, 29 primary cervical carcinomas and 6 normal cervical epithelia" and FGFR3b was "detected in 70 of 76 (92%) bladder carcinomas and 27 of 29 (93%) cervical carcinomas" (see page 18, right column, lines 6-18). In addition, Cappellen et al. teach that said FGFR3 has been determined to have an oncogenic role in other cancers such as myeloma, which was associated with overexpression of FGFR3 (see Cappellan, page 18, middle col.). Thus, there would be a reasonable expectation that it would have a similar function in other cancers.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to practice an *in vitro* method [i] to detect the presence of bladder transitional cell carcinoma (TCC) in an individual or [ii] to assess the stage or severity of bladder TCC in an individual comprising: a) the detection and/or quantification of the FGFR3b protein in a sample of an individual, wherein the sample is a bladder tissue using Western blotting and immunoprecipitation, and b) the comparison of the amount of FGFR3b protein, of detected in a sample of an individual, with their normal reference values; wherein, increased levels of FGFR3b protein relative to normal reference values are indicative of bladder TCC. A skilled artisan would have been motivated to practice such methods because Monia et al. teach that "FGFs and their receptors are expressed at increased levels in several tissues and cell lines and

overexpression is believed to contribute to the malignant phenotype" in other cancers. Also, it would have been obvious for one of skill in the art to compare the expression level of the FGFR3b of a subject to that of a normal patient. A skilled artisan would have had a high expectation of success because protein detection/quantification techniques such as Western blotting and immunoprecipitation, were rampantly used in the equivalent fields as evidenced by Monia et al. and Sturla et al. for the detection of FGFR3 ([a] see above teachings of Monia et al., and [b] see Figure 5 of Sturla et al. on page 1281). As discussed in KSR International Co. v. Teleflex Inc., 550 U.S.--, 82 USPQ2d 1385 (2007), it is considered obvious to combine prior art elements known to be used in equivalent fields of endeavor together into a single combination. The reference clearly shows that the claimed methods were known to be used in equivalent fields of endeavor; thus, it is considered obvious to combine them together. Therefore, the claimed invention as a whole is *prima facie* obvious over the teachings of the prior art.

Although Applicants have argued that Capellen teaches away from the claimed method because "[i]n all the samples with mutated FGFR3, FGFR3b mRNA levels were *similar to or higher than* those encountered in normal bladder and cervix epithelium", thereby leading one to believe that the claimed method is an unreliable way of diagnosing bladder TCC. However, this argument is without any merit because one of skill in the art would have known that there is no direct relationship between the level of expression of the mRNA and the level of expression of its corresponding protein. This

is also acknowledged by Applicants in their remarks on page 7, paragraph 2, filed on 07/15/2010 since Applicants stated that "[t]his fact, which is general knowledge for the skilled person in molecular biology, is clearly demonstrated in Gygi et al., Molecular and Cellular Biology, 9 (3): 1720-1739 Mar 1999 (herewith enclosed), an article which had been cited 335 times in the scientific literature at the end of 2004". As such, regardless of the mRNA levels of FGFR3, one of skill in the art would have been motivated to practice the claimed methods since Monia et al. teach that "FGFs and their receptors are expressed at increased levels in several tissues and cell lines and overexpression is believed to contribute to the malignant phenotype" in other cancers, and Cappellan et al. teach that "[t]he expression of a constitutively activated FGFR3 ... is the first evidence of an oncogenic role for FGFR3 in carcinomas".

In addition, even though Applicants argue that "Sturla cannot be relied on to correct the deficiencies in Capellen, as it is no longer available as prior art," it is noted by the Examiner that, according to MPEP 2131.01 and 2124, the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. The reference of Sturla et al. was used as an evidentiary reference to demonstrate that techniques such as Western blotting and immunoprecipitation, were rampantly used in the equivalent fields as evidenced by Monia et al. and Sturla et al. for the detection/quantification of FGFR3 protein expression. For the reasons provided herein, the claimed invention as a whole is *prima facie* obvious over the teachings of the prior art.

***Conclusion***

Claims 1, 4, 6-12 and 30-38 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656

/SUZANNE M. NOAKES/
Primary Examiner, Art Unit 1656